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(19) (CA) # CANADIAN PATENT

(54) HETEROCYCLIC COMPOUNDS

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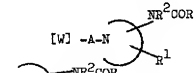
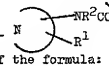
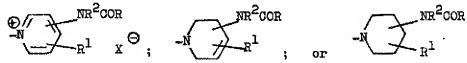
The invention relates to novel heterocyclic compounds, to processes for preparing them and to pharmaceutical compositions containing them.

The present invention provides novel heterocyclic compounds of the general formula:



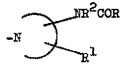
(I)

wherein -  represents a ring system of the formula:



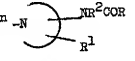
II(a) II(b) II(c)

W represents a cycloalkyl radical containing five to seven ring carbon atoms, or an aryl or heteroaryl radical, all of which radicals may be substituted or unsubstituted, A represents a lower alkylene radical, a mono- or di-keto lower alkylene radical or a hydroxy-lower-alkylene radical, or a bivalent radical of the formula $-O-CH_2CH(OH)CH_2$ or O-(lower-alkylene)-, R represents a substituted or unsubstituted phenyl radical or a cycloalkyl containing from five to seven ring carbon atoms, R^1 represents hydrogen, halogen or lower alkyl, R^2 represents alkyl or aralkyl either of which may be substituted and X denotes an anion, and the acid addition and quaternary ammonium salts of those compounds wherein:



is a ring system of formula II(b) or II(c). The invention also includes the anhydrous forms and the hydrates of the above compounds.

It is to be understood that the term "alkylene" used herein includes both straight and branched chain radicals, the term "lower" when prefixing a radical means the radical concerned contains 1 to 6 carbon atoms, (although those containing 1 to 4 carbon atoms are preferred). By the term "aryl" or heteroaryl radical" is meant a radical possessing aromatic character.

The compounds of formula (I) wherein  is a ring system of formula II(b) or II(c), exhibit one or more of the following pharmacological activities: action on the cardiovascular system (such as hypotensive and/or anti-hypertensive activity), anti-histamine activity and sometimes central nervous system activity (such as sedative or anti-convulsant activities) when tested on warm-blooded animals. The other compounds of formula I are intermediates for corresponding compounds of formula I.

In addition to having useful pharmaceutical properties as mentioned above and the active novel compounds of the invention are intermediates for the preparation of other compounds of formula I.

Examples of W are unsubstituted phenyl or phenyl substituted by one or more groups, which may be the same or different selected from halogen (for example fluorine, chlorine or bromine), lower alkyl (for example

methyl, ethyl, propyl, or butyl), lower alkoxy (for example methoxy, ethoxy, propoxy or butoxy), nitro, amino (including alkyl or dialkyl substituted amino groups in particular dialkylamino, for example dimethylamino or diethylamino), acylamino in particular alkanoylamino [for example acetylamino (acetamido)], hydroxy, carboxyl, lower alkoxycarbonyl, alkylenedioxy (for example methylenedioxy), trihaloalkyl) for example trifluoromethyl), mercapto, methylthio, methylsulphonyl, phenyl and phenyl substituted by one or more of those substituents mentioned immediately above in connection with the substituted phenyl group W. Further examples of W are cycloalkyl (for example cyclohexyl), 1,2,3,4-tetrahydro-naphthyl (for example 1,2,3,4-tetrahydronaphth-6-yl), naphthyl and indenyl radicals which may be substituted or unsubstituted as described above for the substituted phenyl group W, and heterocyclic radicals such as indolyl, thienyl (for example 2-thienyl), benzo[b]thienyl (for example 3-benzo[b]thienyl, furyl, pyrrolyl (for example 3-pyrrolyl), imidazolyl (for example 4-imidazolyl), pyrazolyl (for example 4-pyrazolyl, pyridyl (for example 2- and 4-pyridyl), pyrimidinyl (for example 4-pyrimidinyl), quinolyl (for example 2-quinolyl), thiazolyl (for example 2-, 4- and 5-thiazolyl, isothiazolyl, oxazolyl, isoxazoyl, benzimidazolyl (for example 2-benzimidazolyl, benzo-1,4-dioxanyl (for example benzo-1,4-dioxan-2-yl) and benzindolyl in particular benz[g]indolyl (for example 3-benz[g]-indolyl), which heterocyclic radicals may be unsubstituted

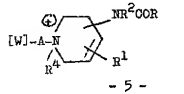
or substituted as described above for the substituted phenyl group W.

Examples of A are methylene, ethylene, propylene, butylene, oxothylene, oxalyl, oxo-propylene, hydroxyethylene and hydroxypropylene. Examples of R^1 are hydrogen, halogen (for example fluorine, chlorine or bromine) and lower alkyl (for example methyl, ethyl, propyl and butyl). Examples of R are the same substituted phenyl radicals as those already described for W and also cyclopentyl, cyclohexyl, cycloheptyl.

Examples of R^2 are lower alkyl groups, e.g., methyl, ethyl, propyl or butyl, or cycloalkyl groups, e.g. cyclopentyl, cyclohexyl and cycloheptyl. The preferred aralkyl groups for R^2 are aryl-lower alkyl, e.g. benzyl and phenethyl.

Examples of acid addition salts are those formed from inorganic and organic acids in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydro-iodide, nitrate, phosphate, sulphonate (such as the methanesulphonate and p-toluenesulphonate), acetate, maleate, fumerate, tartrate and formate.

The quaternary ammonium salts of the compounds of formula I where the quaternizing group is one which can be removed under mild conditions, e.g. by hydrogenolysis are valuable intermediates for the preparation of other compounds of formula I. Preferred quaternary ammonium salts are those of formula (III)

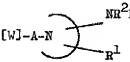


(III)

where the dotted line denotes an optional double bond and R^4 is an arylmethyl radical, e.g. trityl or benzyl, X^- is an anion, e.g. a halide ion, and [W], A, R, R^1 and R^2 are as defined in connection with formula (I).

The compounds of general formula (I) can be prepared in a number of ways by building up the molecule from suitable starting materials in known manner. Such processes applied to the preparation of the novel compounds of formula (I) are included in the scope of the invention.

A preferred method of preparing compounds of formula (I) comprises acylating a compound of the formula (IV)



(IV)

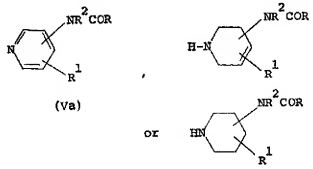
with a reactive derivative of an acid of general formula R.COOH (where R is substituted or unsubstituted phenyl or, cycloalkyl). As a reactive derivative of the acid of formula R.COOH used in the process described above, a halide (for example the chloride or bromide) or an anhydride is preferred. Other examples of reactive derivatives of the acid R.COOH which may be used are the acid azide, mixed anhydrides and active esters. Furthermore the compounds of formula (I) may also be prepared by treating a compound of formula (IV) with the acid R.COOH in the presence of a known condensing agent (for example, a carbodiimide), or by first activating the amino function (for example, by forming the phosphazo derivative and then reacting with the acid R.COOH. In connection with the introduction of the -COR group into a compound of formula (IV) reference may be made to "Chemistry of the Amino Acids" by Greenstein and Winitz (John Wiley & Sons. Inc., Publishers, 1961) at pages 782-883 and 943-1108.

The starting materials of formula (IV) wherein [W] is other than an indolyl radical may be prepared by methods described in our Canadian Patent No. 955,252. Compounds of which [W] is a substituted or unsubstituted indolyl radical may be prepared by methods analogous to those for preparing the other compounds of formula IV.

A preferred method of preparing the compounds of formula (IV) wherein [W] is a substituted or unsubstituted indolyl radical comprises reducing a corresponding compound wherein R^2 is an acyl group. For instance a compound of formula (IV) wherein R^2 is benzoyl may be reduced to a compound of formula (IV) wherein R^2 is benzyl and a compound of formula (IV) wherein R^2 is carbethoxy (CO_2Et) may be reduced to a compound wherein R^2 is CH_3. A suitable reducing agent is lithium aluminium hydride. If the ring system

is unsaturated then this may also be reduced at the same time.

A second method of preparing the compounds of formula (I), comprises reacting a compound of the general formula:



(Va) , (Vb)

or (Vc)

with an alkylating or acylating agent of general formula (VI)

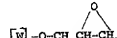
$$[W]\text{-}A\text{-}Y \qquad (VI)$$

(wherein R, R^1, R^2 and W have the meanings given in connection with formula (I)), A is as defined in connection with formula (I) but excluding the radicals mentioned immediately above and Y is a halogen atom or an equivalent replaceable atom or radical for example an organic sulphonyl radical such as a tosyl radical.

Alternatively the compounds of formula Vb or Vc may be reacted with (i) a compound of formula

$$[W]\text{-}A^1\text{-}H \qquad (VII)$$

wherein the chain A^1 contains an epoxide residue for example



$$[W]\text{-}O\text{-}CH_2CH\text{-}CH_2 \qquad (VIII)$$

to give a compound of formula (I) wherein the chain A is substituted by a hydroxyl radical or (ii) a vinyl substituted compound of formula

$$[W]\text{-}B \qquad (IX)$$

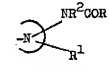
wherein B is a straight or branched chain alkenyl radical, preferably a vinyl radical, to give a corresponding compound of formula (I) wherein A is a straight or branched chain alkylene radical.

The compounds of general formulae (VI), (VII), (VIII) and (IX) are known compounds or can be made following methods known for preparing compounds of these types. The starting materials of general formulae Va, Vb, and Vc can generally be made by acylating a corresponding amino compound of general formula:

(X)

and if necessary reducing the ring system to the corresponding tetrahydropyridine or piperidine ring.

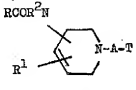
A further method of preparing compounds of formula (I), in which



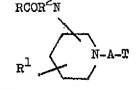
represents a ring system of formula IIb or IIc and A is a lower alkylene or a mono or di-keto lower alkylene radical comprises a Mannich reaction using an aldehyde, a compound of formula Vb or Vc as secondary amine and either a compound WH (where W has the meanings already defined and thus WH can be considered as a compound formed by addition of a hydrogen atom to the radical W;

said compound WH also containing a suitable reactive site of the type known in the literature to participate in the Mannich reaction), or a derivative of W in which the chain A has already been partially formed, and which partially formed chain contains a site of the type known in the literature to participate in the Mannich reaction. Examples of the letter type of derivative are [W]-CH_3, [W]-$CO.CH_3$ and [W]-$(CH_2)_p$-$CH \equiv CH$, wherein p is an integer from 1 to 3 which derivatives are known compounds or can be made following the methods known for preparing compounds of these types. When the derivative is of the third example the product will contain a triple bond in the A chain and this may be hydrogenated to give a compound of formula I in which A is a loweralkylene radical. The aldehyde used in the above reaction may be acetaldehyde or formaldehyde which may be in the form of a solution in an inert solvent as paraformaldehyde, metaldehyde or any other polymeric form or gaseous formaldehyde.

The compounds of general formula (I), may be prepared by starting with a compound of formula:



XIIa

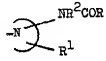


XIIb

wherein T is a known precursor group of W and reacting with another molecule of the type known in the literature for the formation of W. Reference may be made in this connection to standard textbooks of Organic Chemistry

such as: Organic Chemistry by Paul Karrer (Elsevier Publishing Company Inc., 1950); Organic Chemistry by Fieser & Fieser (Reinhold Publishing Corporation 1956); Chemistry of Carbon Compounds by Rodd (Elsevier, Amsterdam, 1951-1969); Heterocyclic Compounds edited by Elderfield (John Wiley & Sons, Inc., 1950-1968); and Chemistry of the Heterocyclic Compounds edited by Weisseberger (Interscience, 1954). As examples of T may be mentioned -COOAlkyl, $-CO.CH_2-OH$ and $-CH_2.CH(OAlkyl)_2$ where Alkyl represents a lower alkyl radical. As examples of reactants known to react with T may be mentioned, o-phenylenediamine, 1-naphthyl-hydrazine or a mixture of formaldehyde and ammonia. The compounds of formula XIIa or XIIb may be made following methods known in the art for the preparation of similar compounds.

A still further process for the preparation of compounds of general formula (I) in which



represents a ring system of formula IIb or IIc, W, R, R^1 and R^2 have the meanings defined in connection with formula (I) and A is a lower alkylene radical, comprises reacting a compound of general formula (XV)

[W]-A-OH (XV)

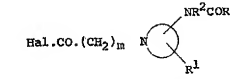
(in which W and A have the meanings defined immediately above) with a compound of formula Vb or Vc (in which R, R^1 and R^2 have the meanings defined immediately above.

The reaction is preferably carried out in the presence of a catalyst, for example Raney Nickel. An organic solvent, which is inert under the reaction conditions, is usually used for example xylene, toluene or benzene. Preferably the reaction is carried out by heating the reactants under reflux in a water-immiscible organic solvent, for example xylene, and removing the water formed during the reaction by azeotropic distillation. If necessary, reactive substituent groups can be blocked during a reaction and released later.

In order to prepare a compound of formula (I) wherein A is a mono-keto lower-alkylene radical of formula $-CO.(CH_2)m$ in which m is 1 to 5, a compound of formula:

[W]-H (XVI)

can be acylated (Friedel-Crafts) with an acid halide of formula:



(XVII)

For details of the reaction reference may be made to "The Friedel-Crafts and related reactions" by G.A. Olah Vol. 3 (Interscience Publishers, 1964).

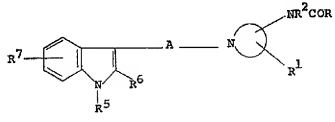
Certain compounds of formula (I) may also be prepared by treating a compound of formula (III) as defined above under mild conditions such as to remove the group R^4. Preferably the group R^4 is removed by hydrogenolysis under standard conditions e.g. using an appropriate catalyst such as a palladium on carbon catalyst, a platinum catalyst or a nickel catalyst. In this reaction a mono or diketo lower alkylene radical A may also be reduced to a corresponding hydroxy lower alkylene radical A. If the keto compound is desired it can be obtained by oxidation of the final product. When hydrogenolysis is used to remove the group R^4 and the optional double bond is present in the heterocyclic ring (i.e. a tetrahydropyridine compound is used) this double bond will be reduced so that the final product is a piperidine compound of formula (I). If a compound of formula (I) in which the optional double bond is present is desired this can be obtained by treating compound (III) under other conditions effective to remove R^4 without saturating the double bond.

Instead of a compound of formula (III) wherein R^4 is as defined above any other starting material where R^4 is an organic group which can be readily removed under mild conditions can be used.

Other conditions which may be effective to remove the group R^4 are treatment with acid e.g. with acetic acid or hydrochloric acid to remove a trityl group or treatment with alkali metal in liquid ammonia.

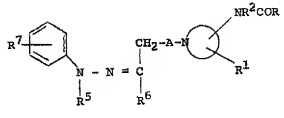
The preferred groups R^4 in the starting material of formula (III) are arylmethyl radicals such as benzyl, diphenylmethyl, trityl or naphthylmethyl.

Compounds of formula (I) in which [Y] is a substituted or unsubstituted indolyl radical for example compounds of formula



(XVIII)

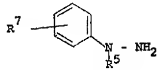
wherein R, R^1, R^2 and A are as defined in connection with formula I, R^5 represents hydrogen, lower alkyl, lower aralkyl or aroyl, R^6 represents hydrogen, lower alkyl, or aryl, R^7 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl, may also be prepared by carrying out a Fischer indole synthesis on a compound of general formula



(XIX)

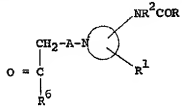
wherein R, R^1, R^2, R^5, R^6, R^7 and A are as defined immediately above.

The starting material can be prepared by condensing a phenyl hydrazine of formula



(XX)

with an aldehyde or ketone of general formula



(XXI)

in which formulae R, R^1, R^2, R^5, R^6, R^7 and A are as defined above. The compounds of formula (IV) wherein [W] is a substituted or unsubstituted indolyl radical may also be prepared by a Fischer indole synthesis analogous to that just described.

The reactions outlined above usually are carried out in a solvent which is inert under the reaction conditions, for example an alcohol such as methanol, ethanol or propan-2-ol, ether, dioxane, dimethyl-formamide, pyridine, water, dimethoxyethane, methylene chloride, tetrahydrofuran and acetic acid or mixtures of such solvents. The most suitable solvent system is chosen and varies depending on the particular reactants being employed. If necessary heating the reactants in solution under reflux can be carried out, and if necessary heating under high pressures may also be used.

Once a compound of general formula (I) has been prepared, then if necessary one or more substituents in the molecule

may be converted to another substituent each within its own meanings specified in connection with formula (I). If a compound is produced in which  represents the pyridinium ring system of formula II(a), this may be selectively reduced to one of the other ring systems of lower oxidation state. For example, reduction with an alkali metal borohydride gives the tetrahydropyridine ring system of formula II(b). On the other hand, catalytic hydrogenation, for example, in the presence of Raney nickel or a platinum catalyst, or careful reduction with a hydride transfer agent (such as lithium aluminium hydride) gives rise to the piperidine ring system of formula II(c). Similarly if a compound of formula (I) is prepared in which  represents the tetrahydropyridine ring system of formula II(b), this may also be reduced to the piperidine ring system of formula II(c).

If a compound of formula (I) is prepared in which the chain A contains one or more carbonyl functions, then this chain may be selectively reduced. For example,

when A is the oxalyl residue -CO.CO-, this may be reduced under mild conditions such as by a hydride transfer agent (particularly lithium aluminium hydride) to give the $-\underset{OH}{CH}-CH_2$ residue. When A is the $-CO-CH_2-$ residue this may be reduced with an alkali metal borohydride to give the $-\underset{OH}{CH}.CH_2-$ residue. When the oxalyl residue is reduced under more drastic conditions, the ethylene chain $-CH_2-CH_2-$ results.

A compound of formula I may be hydrolysed to remove the COR group and the product may then be acylated to give a compound of formula I with a different COR group.

When a compound of formula (I) is produced wherein the radical W has one or more methoxy substituents, hydrolysis to the corresponding hydroxyl compound may be brought about in known manner. Furthermore, if the radical W has a nitro substituent this may be reduced in known manner to the corresponding amino compound which in turn may be further acylated or alkylated.

If necessary, in any of the reactions hereinbefore described, reactive substituent groups may be blocked during a reaction and released at a later stage. As already indicated the novel tetrahydropyridine and piperidine compounds provided by the invention contain a basic nitrogen atom and thus can form acid addition salts with acids (particularly pharmaceutically acceptable acids) or quaternary ammonium salts, for example with alkyl halides or aralkyl halides (particularly methyl iodide or benzyl chloride or bromide). The acid addition salts may either be formed in situ during the hereinbefore described processes and isolated therefrom or a free base may be treated with the appropriate acid

in the presence of a suitable solvent and then the salt isolated. The quaternary salts may be prepared by treating the free base with the appropriate halide in the presence or absence of a solvent.

The invention also includes pharmaceutical compositions containing as active ingredient an active compound of formula I as above defined. The active compound may be micronised if desired. In addition to the active ingredient, the compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10-80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formation of an active ingredient with encapsulating

material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition,

the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 5 mg. or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The following non-limiting Examples illustrate the invention:

EXAMPLE 1

3-[2-(4-Ethoxycarbonylamino-1-piperidyl)-ethyl]-indole

4-Amino-1-[2-(3-indolyl)ethyl]piperidine (1.3 g.) was dissolved in methylene dichloride (250 ml) containing triethylamine (0.51 g) and to the stirred solution was added ethyl chloroformate (0.54 g.) in methylene chloride (15 ml) over 5 minutes. Stirring was continued for 2 hours. The mixture was extracted with water (2 x 50 ml) and the organic phase separated, dried ($MgSO_4$) and evaporated to give an oil. Trituration in ether afforded the title compound as the hydrate, a cream solid (0.87 g.) which recrystallised from aqueous ethanol as colourless needles, m.p. 80-82°. Found: C,63.34; H,8.35; N,12.04. $C_{18}H_{25}N_3O_2.1\frac{1}{2}H_2O$ requires C,63.13; H,8.24; N,12.27%.

EXAMPLE 2

3-[2-(4-Methylamino-1-piperidyl)ethyl]-indole

3-[2-(4-Ethoxycarbonylamino-1-piperidyl)ethyl]-indole,

hydrate (7.96 g.) was added portionwise to a stirred suspension of lithium aluminium hydride (10.0 g.) in 1,2-dimethoxyethane (250 ml) and the mixture refluxed for 4 hours. Water (30 ml) was added dropwise to decompose unchanged hydride and the mixture filtered and evaporated to give the required product as an oil which solidified on trituration in ether (1.21 g.). A portion of this was converted to the hydrochloride (needles from ethanolic HCl/ether), m.p. 251.1°. Found: C,57.10; H,7.61; N,12.20. $C_{16}H_{23}N_3.2\ HCl.1/4H_2O$ requires C,57.40; H,7.68; N,12.55%.

EXAMPLE 3

3-[2-(4-N-Methylbenzamido-1-piperidyl)ethyl]-indole

3-[2-(4-Methylamino-1-piperidyl)ethyl] indole (free base from Example 2) (5.05 g.) was dissolved in chloroform (100 ml) and a solution of potassium carbonate (2.72 g.) in water (100 ml) added. To the stirred mixture was added dropwise a solution of benzoyl chloride (2.76 g.) in chloroform (50 ml). Stirring was continued for 1 hour, the chloroform phase was separated and the aqueous phase re-extracted with chloroform (50 ml). The combined organic phases were dried ($MgSO_4$), treated with charcoal, filtered and evaporated to give an oil which crystallised on standing. This was dissolved in ethanol-HCl and ethyl acetate added until crystallisation commenced. Filtration afforded the title compound in the form of the hydrochloride as colourless needles (6.43 g.), m.p. 216-218°. Found: C,69.27; H,7.08; N,10.33. $C_{23}H_{27}N_3O.HCl$ requires C,69.41; H,7.09; N,10.56%.

EXAMPLE 4

5-Benzyloxy-3-[2-(4-[N-Benzylbenzamido] piperidono)ethyl] indole

A. 5-Benzyloxyindole-3-glyoxyloyl chloride (23.2 g.) was added portionwise to a stirred solution of 4-benzamido-piperidine (30.2 g.) in dry 1,2-dimethoxyethane (1200 ml.). After 1 hour the resulting solid was collected, suspended in water (1 l.) and stirred for 1 hour. The product was filtered off, washed, and dried to give 4-benzamido-1-(5-benzyloxyindole-3-glyoxyloyl)piperidine (34.49 g.) m.p. 264° (Found C,71.85; H,5.67; N,8.66. $C_{29}H_{27}N_3O_4$ requires C,72.33; H,5.65; N,8.73%).

B. The foregoing product (33.88g.) was added portionwise to a stirred refluxing suspension of lithium aluminium hydride (20 g.) in dry tetrahydrofuran (850 ml.) Stirring and refluxing were continued for 4 hours, then water (20 ml.) and 2N sodium hydroxide solution (40 ml.) were added carefully dropwise. Stirring was continued for a further 20 minutes, then the mixture was filtered and the inorganic material was washed well with fresh tetrahydrofuran.

The combined filtrate and washings were evaporated and the residual oil was dissolved in hot ethanol and made just acid with ethanolic HCl to give 3-[2-(4-benzylaminopiperidino)-ethyl-5-benzyloxyindole, dihydrochloride, hemihydrate (31.03 g.) m.p. 210° (Found C, 66.75; H, 6.71; N, 7.95. $C_{29}H_{33}N_3O$. $2HCl.\frac{1}{2}H_2O$ requires C, 66.78; H, 6.96; N, 8.06%).

C. The foregoing product (2.61 g.) and potassium carbonate (2.76 g.) were stirred with water (50 ml) and methylene chloride (50 ml) until dissolved. Benzoyl chloride (850 mg) was added dropwise and stirring was continued for 1 hour. The aqueous phase was separated and reextracted with methylene chloride and the combined organic layers were dried and evaporated. Treatment of the residual oil with ethanolic HCl provided the title compound as a hydrochloride hemihydrate (2.52g.) m.p., 265° (decomp.). (Found: C, 73.64; H, 6.78; N, 6.98; $C_{36}H_{37}N_3O_2.HCl.\frac{1}{2}H_2O$ requires C, 73.39; H, 6.67; N, 7.13%).

EXAMPLE 5.

5-Hydroxy-3-[2-(4-benzylbenzamido)-1-piperidyl)ethyl]indole

Part C of Example 4 was repeated but without the final conversion to the hydrochloride and the base (1.40 g.) in acetic acid (25 ml.) was hydrogenated in the presence of 5% palladium charcoal at 50° and 50 p.s.i. for 6 hours. The reaction mixture was cooled, filtered and evaporated. Treatment of the residue with ethanolic HCl gave the product hydrochloride (860 mg) which was recrystallised from aqueous ethanol to give the title compound hydrochloride hydrate as pale pink prisms, m.p. 180°. (Found C, 68.44; H, 6.64; N, 8.19. $C_{29}H_{31}N_3O_2$,HCl.H_2O requires: C, 68.55; H, 6.75; N, 8.27%).

EXAMPLE 6

2-[2-(4-N-Methylbenzamido-1-piperidyl)ethyl]naphthalene

4-Amino-1-[2-(2-naphthyl)ethyl]piperidine is acylated with ethyl chloroformate following the conditions of Example 1 to give the ethoxycarbonylamino derivative which is reduced following the conditions of Example 2 to the corresponding N-methylamine. Benzoylation following the conditions of Example 3 then provides the title compound in the form of the hydrochloride m.p. 283.2° (Found: C, 73.44; H, 7.17; N, 6.9. $C_{25}H_{28}N_2O$.HCl requires: C, 73.41; H, 7.15 N, 6.85%).

EXAMPLE 7

N-[1-(3-Benzoylpropyl)-4-piperidyl]-N-methylbenzamide

Following the conditions of Example 6 but utilising 4-amino-1-(3-benzoylpropyl)piperidine in place of 4-amino-1-[2-(2-naphthyl)ethyl]piperidine, the title compound hydrochloride is obtained.

EXAMPLE 8

N-[2-(4-Pyridyl)ethyl-4-piperidyl]-N-methylbenzamide.

The title compound is prepared from 4-amino-1-[2-(4-pyridyl)ethyl]piperidine following the conditions of Examples 6 and 7.

EXAMPLE 9

3-[2-(4-N-Ethylbenzamido-1-piperidyl)ethyl]indole.

A. 4-Acetamido-1-[2-(3-indolyl)ethyl]piperidine is reduced with lithium aluminium hydride following the conditions of Example 2 to give 3-[2-(4-ethylamino-1-piperidyl)ethyl]indole.

B. The foregoing amine is benzoylated under the conditions of Example 3 to give the title compound hydrochloride.

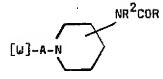
EXAMPLE 10

1-[2-(cyclohexyl)ethyl]-4(N-methylbenzamido)piperidine.

4-Methylamino-1-[2-cyclohexylethyl]piperidine is treated with benzoyl chloride following the procedure of Example 3 to give the title compound which is isolated as the hydrochloride.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

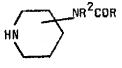
1. A process for preparing heterocyclic compounds of formula



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein W represents a cycloalkyl radical containing five to seven ring carbon atoms, or a phenyl, naphthyl, indolyl or pyridyl radical, any of which radicals may be unsubstituted or substituted by one or more groups selected from halogen, lower alkyl, lower alkoxy, hydroxy or benzyloxy; R represents a phenyl radical; R^2 represents a lower alkyl or phenyl lower alkyl radical; and A represents a lower alkylene or mono keto lower alkylene radical which comprises

(i) reacting a compound of formula



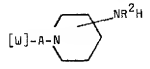
(V)

wherein R^2 and R are as defined above, with an alkylating or acylating agent of general formula (VI)

[W]-A-Y (VI)

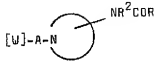
wherein W and A are as defined above and Y is a halogen atom or an equivalent replaceable atom or radical,

(ii) reacting a compound of formula

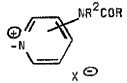


wherein W, A and R^2 are as defined above, with an acylating agent containing the group RCO wherein R is as defined above, or

(iii) selectively reducing a compound of formula

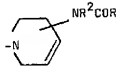


wherein W, R and R^2 are as defined above, A represents lower alkylene, and  represents a ring system of formula:



II(a)

or



II(b)

wherein $X^{\ominus}$ is an anion.

2. A process according to Claim 1 wherein R^2 is methyl.

3. A process according to Claim 1 wherein the acylating agent containing the group RCO is a benzoyl halide.

4. A process according to Claim 1 wherein A represents $-CH_2CH_2-$ or $-COCH_2CH_2CH_2-$.

5. A heterocyclic compound of formula I whenever prepared by a process as claimed in Claim 1 or by an obvious chemical equivalent thereof.

6. A heterocyclic compound of formula I whenever prepared by a process as claimed in Claim 2 or by an obvious chemical equivalent thereof.

7. A heterocyclic compound of formula I whenever prepared by a process as claimed in Claim 3 or by an obvious chemical equivalent thereof.

8. A heterocyclic compound of formula I whenever prepared by a process as claimed in Claim 4 or by an obvious chemical equivalent thereof.

9. A process for preparing 3-[2-(4-N-methylbenzamido-1-piperidyl)ethyl]indole which comprises acylating 3-[2-(4-N-methylamino-1-piperidyl)ethyl]indole with a benzoyl halide and if desired isolating the product as the free base or a pharmaceutically acceptable acid addition salt thereof.

10. 3-[2-(H-N-methylbenzamido-1-piperidyl)ethyl]indole or a pharmaceutically acceptable acid addition salt thereof whenever prepared by a process as claimed in Claim 9 or by an obvious chemical equivalent thereof.

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